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Rosiglitazone Increases Small Dense LDL Concentration and Decreases HDL Particle Size in HIV-infected Patients

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Summary

This study evaluated the effects of rosiglitazone on lipid particle size in HIV-infected patients with lipoatrophy. Following 12 weeks of rosiglitazone (vs. placebo), significant increases in total and small dense LDL, and total:HDL cholesterol ratio were found. Large HDL concentration and HDL particle size decreased significantly with rosiglitazone compared to placebo. These data indicate the production of a more atherogenic lipid profile with rosiglitazone, a consideration when selecting treatment for the growing population of HIV-infected patients with type-2 diabetes and dyslipidemia.

Keywords

Rosiglitazone; small dense LDL; HDL particle size

Introduction

Rosiglitazone is a PPAR- γ agonist recognized for its ability to improve glycemic control and insulin sensitivity. Studies of rosiglitazone in HIV-associated lipoatrophy show improvements in insulin sensitivity [1–6], and in several studies increases in subcutaneous adipose tissue [3–5, 7]. However, undesirable changes of lipid profiles with rosiglitazone were often documented [1–6]. The utility of rosiglitazone for insulin resistance and diabetes in HIV may therefore be limited by its effects on lipids. The negative effect of PPAR- γ agonist on lipid profile may be ameliorated though by specific effects on lipid particle size and changes in atherogenic lipoprotein subclasses. For example, data in type 2 diabetes suggest that some thiazolidinediones increase large LDL cholesterol and LDL particle size [8–10].

We previously reported the results of a randomized placebo controlled trial of rosiglitazone which showed significant increases in total and LDL cholesterol (LDL-C) in HIV-infected

subjects with lipodystrophy[3]. Here, we present new data on lipoprotein particle size and subclass concentrations demonstrating a pro-atherogenic effect of rosiglitazone on lipid profile in HIV to a degree not previously appreciated.

Methods

Metabolic and body composition results of the randomized placebo controlled 12 week trial of rosiglitazone (4mg/day) for HIV-infected men and women (n=28) with lipoatrophy and insulin resistance were reported previously [3]. Here we present data on lipid profile and nuclear magnetic resonance (NMR) spectroscopy of lipoprotein size, particle concentration, and subclass concentration (Liposcience, Raleigh, N.C., USA) obtained at baseline and 12 weeks. The methodology employed by Liposcience is described in detail elsewhere [11]. Written informed consent was obtained from each subject prior to the study

Statistical Analyses—Baseline characteristics were compared between randomization groups using the Student *t*-test for continuous variables and chi-square statistics for non-continuous variables. Within each group, changes over 12-weeks were calculated by subtracting baseline values from end of study values. The effect of treatment was assessed by performing Student *t*-test on the calculated change scores. Non-parametric Wilcoxon rank sum test was used where change scores were non-normally distributed. Additional analyses were performed to adjust for exposure to lipid lowering medications. All values are presented as mean (SEM), and statistical significance was accepted at the $p < 0.05$ level. Statistical analyses were performed using SAS JMP software, version 6.0 (SAS Institute, Inc., Cary, North Carolina).

Results

There were no significant differences between groups for age, duration of HIV, duration of antiretroviral therapy, protease inhibitor use, body mass index, CD4⁺ t-cell cell count or the percentage of subjects with HIV viral RNA levels below the limit of detection. Six subjects randomized to placebo, and 9 randomized to rosiglitazone were on lipid lowering medications during the study; one subject on rosiglitazone commenced a lipid lowering medication during the study.

There were no significant differences between groups in total VLDL, LDL or HDL concentrations nor mean lipoprotein particle size at baseline. Further, subclass concentrations of VLDL, LDL, and IDL were not different at baseline, (Table 1). Total LDL and IDL concentrations increased with rosiglitazone compared to placebo, whereas total HDL and VLDL did not change. Mean VLDL and LDL particle sizes did not change, but mean HDL particle size decreased in the rosiglitazone vs. placebo-treated group.

Small LDL and very small LDL increased significantly with rosiglitazone compared to placebo, whereas large HDL decreased. There was also a significant difference in the change in cholesterol:HDL cholesterol ratio (mean change with rosiglitazone +1.02 [0.41] vs -1.23 [0.40] with placebo, $p=0.0006$). In all cases, the significant differences noted between treatment groups remained significant after the analyses were adjusted for exposure to lipid lowering therapy.

Discussion

Lipid abnormalities are common among HIV-infected patients on antiretroviral therapy [12, 13]. In the present study, rosiglitazone, given to improve lipoatrophy and insulin resistance, worsened lipid profile in HIV-infected subjects by increasing the concentration of smaller LDL particles, and decreasing large HDL concentration and HDL mean particle size.

Increases in LDL-C with the use of rosiglitazone are well-documented in studies of diabetes [14] [15] and in HIV [1–6]. In a meta-analysis of the effects of thiazolidinediones on cardiovascular disease risk in diabetes, Chiquette et al.[14] identified a mean increase LDL-C of 15 mg/dl (95% CI 13–18 mg/dl). We previously reported a 0.4 mmol/L (15 mg/dl) increase in LDL-C in this study of rosiglitazone for HIV lipoatrophy [3] which is similar to LDL-C increases reported in other trials in HIV (range 7–30 mg/dl) [2, 4, 5] The significance of this modest increase and the impact on overall cardiovascular disease risk, however, is more fully appreciated when lipid particle subpopulations are assessed.

Prospective, population-based studies in the general population have shown that small, dense LDL particles are associated with increased risk of coronary artery disease [16]. Different PPAR- γ agonists may have different effects on LDL particle size. For example, troglitazone use increased large LDL and mean LDL particle size after 8 weeks of treatment for type-2 diabetes [8]. Reductions in small dense LDL are reported with pioglitazone in patients with type 2 diabetes and hypertension [10, 17]. In a large study of type 2 diabetes and hyperlipidemia, both rosiglitazone and pioglitazone led to increased LDL particle size, but with a greater effect of pioglitazone[18]. In contrast, in the current study, rosiglitazone was associated with significant increases in small dense LDL particles compared to placebo, thereby shifting patients to a more atherogenic lipid profile. These data suggest that thiazolidinediones have varying effects on lipids, not only on overall lipid profile [14], but potentially important different effects on lipoprotein size and particle subclasses.

We also identified a significant reduction in HDL size and increases in IDL with rosiglitazone versus placebo. Stein et al. [19] previously reported decreased HDL particle size in HIV-infected patients compared to controls, and this decrease was present irrespective of protease inhibitor use. Therefore decreases in HDL size and the reduction in total cholesterol:HDL cholesterol ratio with rosiglitazone marks a further exacerbation of the dyslipidemia present at baseline in this population.

This was a relatively small study and use of lipid lowering therapy was not exclusionary, however, both treatment groups had a similar percentage of patients on lipid lowering therapy. Statistical adjustment for the use of lipid lowering therapies did not alter the significant findings in this study.

This study indicates a shift towards a more atherogenic lipid profile with the addition of rosiglitazone in patients with HIV, lipoatrophy and insulin resistance. The deleterious effects of rosiglitazone on lipids is one mechanism believed to contribute to the increased risk of MI associated with its use observed in a recent meta-analysis of controlled trials [20]. Our findings suggest that lipid parameters and management of dyslipidemia should be taken into consideration when selecting a PPAR- γ agonist to treat insulin resistance or diabetes in HIV.

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Baseline Values and Changes in NMR Determined Lipid Parameters after 12 weeks Rosiglitazone Therapy Compared to Placebo (n=28)

Table 1

	Placebo (n=12)		Rosiglitazone (n=16)		p-value
	Baseline	Change	Baseline	Change	
VLDL Particles (nmol/L)					
Total	123.2 ± 14.1	-2.6 ± 14.5	127.9 ± 15.7	23.5 ± 10.8	0.15
Large	30.7 ± 7.4	-0.9 ± 3.3	15.1 ± 4.0	5.3 ± 2.4	0.13
Medium	58.3 ± 10.0	-1.6 ± 12.9	70.1 ± 9.2	4.0 ± 8.4	0.71
Small	34.2 ± 5.9	-0.1 ± 6.5	42.7 ± 6.5	14.3 ± 6.9	0.15
IDL Particles (nmol/L)					
	60.7 ± 10.9	-18.6 ± 9.2	42.6 ± 11.4	8.3 ± 8.6	0.04
LDL Particles (nmol/L)					
Total	1670.8 ± 205.6	-200.4 ± 76.9	1422.3 ± 129.3	242.3 ± 112.5	0.006
Large	157.9 ± 42.9	57.3 ± 39.1	242.2 ± 66.1	103.7 ± 103.9	0.71
Small (total)	1452.3 ± 181.4	-239.0 ± 102.7	1137.6 ± 148.3	130.4 ± 127.8	0.04
Medium Small	293.2 ± 32.3	-34.6 ± 21.8	238.7 ± 29.9	8.50 ± 25.7	0.23
Very Small	1159.2 ± 150.2	-204.3 ± 86.6	899 ± 119.1	121.6 ± 103.7	0.03
HDL Particles (μmol/L)					
Total	25.7 ± 1.32	1.0 ± 1.1	29.8 ± 1.8	-2.1 ± 1.5	0.12
Large	1.87 ± 0.61	0.54 ± 0.4	3.05 ± 0.80	-1.13 ± 0.6	0.03
Medium	7.3 ± 1.5	1.4 ± 1.4	4.5 ± 1.1	3.3 ± 1.3	0.31
Small*	16.5 ± 1.3	-0.9 ± 1.3	22.3 ± 1.5	-4.3 ± 1.9	0.17
Mean Particle Size (nm)					
VLDL	63.3 ± 4.2	2.3 ± 1.9	58.7 ± 3.3	0.2 ± 2.2	0.50
LDL	19.8 ± 0.1	0.28 ± 0.16	20.2 ± 0.2	-0.03 ± 0.18	0.23
HDL	8.51 ± 0.10	0.21 ± 0.07	8.63 ± 0.09	-0.65 ± 0.49	0.003

Values expressed are mean ± SEM.

* Significant difference between treatment groups at baseline (p<0.01).